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Blinded and uniform cause of death verification in a lung cancer CT screening trial[☆]

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ABSTRACT

Disease-specific mortality is the final outcome of a lung cancer screening trial, therefore cause of death verification is crucial. The use of death certificates for this purpose is debated because of bias, inaccurate completion and incorrect ante mortem diagnoses. A cause of death evaluation process was designed to ensure a uniform and unbiased determination of the graduation of certainty that lung cancer was the underlying cause of death. An independent clinical expert committee will review the medical files of all deceased participants once diagnosed with lung cancer and will make use of a flow chart and predetermined criteria. A pilot study of fifty cases was conducted to determine the performance of this process and to compare the outcome with the official death certificates. The independent review has shown an agreement of 90% (kappa 0.65), which demonstrates a uniform classification. The sensitivity and specificity of the death certificates for lung cancer specific mortality were 95.2 and 62.5%. This demonstrates a limited distinctive character of the death certification process in lung cancer patients. Our results imply that the final outcome of a lung cancer screening trial cannot reliably be established without predetermined criteria and an independent review of blinded cases.

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1. Introduction

Lung cancer is the first cause of cancer-related death in males and the second in females globally, accounting for 1.4 million deaths per year [1]. Despite treatment advances, survival has not improved substantially over the past 30 years, mainly because the majority of the patients have distant metastasis at the time of diagnosis [2]. The early detection of lung cancer by screening asymptomatic smokers with low dose computer tomography (CT) scanning is a promising strategy to reduce lung cancer mortality,

since the results of the National Lung Screening Trial (NLST) were published [3,4].

Disease-specific mortality is the outcome of lung cancer screening; therefore, cause of death (CoD) verification is crucial. The use of death certificates for this purpose is debated for several reasons. Firstly, two forms of bias especially affect death certification in screening trials. Sticky-diagnosis bias; because lung cancer is more likely to be diagnosed in the screen arm, deaths are more likely to be attributed to lung cancer compared to the usual care arm [5]. Slippery-linkage bias; deaths as a result of interventions for lung cancer may be difficult to trace back to screening and could easily be certified as death due to other causes [5]. Secondly, the merit of death certificates depends on the accuracy of the certifying clinician and nosologist and the establishment of a correct ante mortem diagnosis [6,7]. Common reasons for misclassification are coinciding malignancies, considerable comorbidity and death after a surgical procedure [8,9]. Finally, the sensitivity and specificity of the death certificate has been reported to range from 84.5 to 99.7%

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and 91.3 to 99.7%; causing an error that tends to reduce the effect of screening [9–12].

To overcome these problems clinical expert committees (CEC), reviewing the medical files of the deceased participants to determine the cause of death, are frequently employed in cancer screening trials [9–14]. The additional value of a CEC depends on the use of predetermined criteria and a thorough and independent evaluation of all cases with lung cancer blind towards each arm, to prevent an unbalanced outcome between the study arms.

We hypothesized that a clinical expert committee cannot reliably establish the outcome of a lung cancer screening trial, unless they are independent and review the medical files blinded and with predetermined criteria and flowcharts. The aim of this study is to develop a CoD review process protocol that will be used in the Dutch-Belgian lung cancer CT screening trial (NELSON). The performance of the protocol has been tested in a pilot and the outcomes will be compared with the official death certificates.

2. Methods

2.1. Study design and subjects for the NELSON trial

Details of the design and conduct of the Dutch-Belgian lung cancer screening trial have been reported elsewhere [15,16]. Briefly, randomly assigned eligible participants underwent CT screening at baseline (first round), 1 year later (second round), 3 years later (third round) and 5.5-year later (fourth round) or no screening. The purpose of the trial is to determine whether at 10 years after randomisation, CT screening will have reduced mortality from lung cancer by at least 25% [16]. The trial was approved by the Dutch Minister of Health and the ethics board at each participating centre [4]. All participants provided written informed consent for the evaluation of personal data from hospital charts and national registers. The CoD evaluation process of the NELSON trial was designed to ensure a uniform and unbiased determination of the primary cause of death in participants with lung cancer.

2.2. Identification of subjects for the CoD review and data collection

The cause of death of all participants of the NELSON trial that are diagnosed with lung cancer (during their lifetime or at autopsy) are subject of the 'review process' to ensure a valid determination of the primary outcome measure of the screening trial. The lung cancer cases are identified by linkages with the national cancer registries of the Netherlands and Belgium and by checking all official death certificates for the diagnosis lung cancer, which are obtained from Statistics Netherlands and the Flemish Agency for Care and Health. For all identified cases, the diagnosis of lung cancer is verified by a pathology panel [17] or clinical experts for cases without cytology or histology. This verification process of the lung cancer diagnosis was performed separately from the CoD-verification process in the NELSON-trial and will not be addressed in this manuscript.

After the identification of the subjects, all relevant medical information will be collected and blinded for the participant's identity and study arm by an individual who is not otherwise involved in the trial. The medical files include: information provided by the general practitioner, discharge, outpatient visit letters, reports of radiology, nuclear medicine, pathology and microbiology, laboratory results, and autopsy reports.

2.3. Formation of the clinical expert committee

All cases will be reviewed and classified separately by the three members of the CEC, who are no employees of the screening trial. The committee is formed by a pulmonologist–oncologist and

Table 1
Classification of the cause of death.

Cause of death	Definition
Definitely lung cancer death	Death certainly as a direct result of (second primary) lung cancer, a paraneoplastic syndrome or a diagnostic or therapeutic intervention, including euthanasia and palliative sedation. No clear other cause of death is present.
Probable lung cancer death	Participants with (second primary) lung cancer with evidence of locoregional or distant disease progression or a paraneoplastic syndrome. It is uncertain whether this is the final direct cause of death. No clear other cause of death is present.
Possible lung cancer death	Participants with (second primary) lung cancer with evidence of locoregional or distant disease progression or a paraneoplastic syndrome and one or more coinciding malignancies. It is not possible to determine which malignancy was the primary cause of death.
Unlikely lung cancer death	Participants with (second primary) lung cancer, but without evidence of locoregional or distant disease progression, a paraneoplastic syndrome or death as a result of an intervention for lung cancer. No clear other cause of death is present.
Definitely no lung cancer death	The cause of death is definitely not a direct or indirect result from (second primary) lung cancer, a paraneoplastic syndrome or an intervention for lung cancer. Another cause of death is present.
Intercurrent death with lung cancer as contributing factor	Only use this option when the cause of death cannot be classified as listed above. The cause of death is definitely not a direct result from (second primary) lung cancer. Another cause of death is present and lung cancer contributed to the death of the patient.

pathologist specialised in lung oncology and a clinical epidemiologist specialised in screening. For a random sample of 10%, cases with disagreement and all intervention related deaths the committee will meet. An international committee will be consulted in case no consensus is reached.

2.4. The cause of death evaluation process protocol

The evaluation process performed by the experts will be guided by the use a flowchart (Fig. 1a–d in the supplementary data) and a detailed list of criteria (Appendix 1 in the supplementary data). The product of the evaluation is the classification of the cause of death of the participant in one of the six categories which define graduation of certainty that lung cancer was the primary cause of death (Table 1).

2.5. Design and subjects of the CoD pilot

Before the implementation of the protocol we decided to perform a pilot study by ourselves with a limited number of cases to test its user-friendliness and performance compared with the official death certificates. Therefore, we included the first fifty consecutive deceased participants diagnosed with lung cancer. In contrary to the CEC of externals to be formed for the review of all lung cancer deaths, a medical doctor (N.H.) and a clinical epidemiologist (H.J.d.K), internals of the NELSON-trial formed the committee for the pilot study. The collection and blinding of the medical files and the review process itself was performed as described. After the completion of the evaluation of the cases by both reviewers separately, the reviewers met and discussed the cases with disagreement. Two of the pulmonologist–oncologists of the NELSON

Table 2
Characteristics of the fifty subjects of the pilot study.

Age ^a	Mean: 62.6 years Range: 51–73 years
Gender	Male: 42/50 (84%) Female: 8/50 (16%)
Base for the diagnosis lung cancer	Surgical resection of primary tumor: 16/50 (32%) Histology or cytology of primary tumor: 15/50 (30%) Histology or cytology of lymph node metastasis: 6/50 (12%) Histology or cytology of distant metastasis: 8/50 (16%) Autopsy: 1/50 (2%) Clinical picture and imaging techniques: 4/50 (8%)
Disease stage at diagnosis ^b	IA: 12/50 (24%) IIA: 2/50 (4%) IIB: 1/50 (2%) IIIA: 6/50 (12%) IIIB: 3/50 (6%) IV: 26/50 (52%)

^a Age at the inclusion in the NELSON trial.

^b TNM staging system for lung cancer 7th edition.

trial (H.J.M.G. and J.-W.J.L.) were consulted in case of persistent disagreement. After that, the final outcome of the pilot study was compared with the primary cause of death on the official death certificate.

2.6. Analysis

The primary cause of death is defined as ‘the disease that initiated the chain of morbid events directly leading to death’. Lung cancer mortality, the primary endpoint of the study, is defined as “definitely” or “probable lung cancer death” (Table 1). “Possible”, “unlikely” and “definitely no lung cancer death” and “intercurrent death with lung cancer as a contributing factor” are considered as death due to other causes (Table 1).

The agreement between the two reviewers of the CoD pilot is assessed by means of kappa statistics. A kappa of 1 and 0, respectively indicates a perfect agreement and no agreement.

The cause of death, as assigned by the review committee of the pilot after consensus meeting, is considered as the gold standard. The sensitivity and specificity of the official death certificates were defined as the proportion of lung cancer deaths assigned by both sources and as death due to other causes.

Because it is not yet allowed to analyse the data by study arm, no absolute numbers of lung cancer deaths per arm are disclosed. Therefore, it is not possible to determine if the CoD review process enhances or attenuates the effect of screening.

3. Results

The baseline characteristics, base for the diagnosis of lung cancer and the disease stage of the fifty subjects that were included in the pilot are displayed in Table 2. The separate classification of the cause of death by the reviewers is shown in Table 3. In thirty-eight of the fifty participants (76%) the reviewers reached a concordant conclusion. The twelve remaining cases with disagreement had; significant comorbidity (3), multiple malignancies (2), death after an intervention (3) and death indirectly caused by lung cancer (4), such as death due to post-obstruction pneumonia or paraneoplastic pulmonary embolism. However, when clustering all “definitely” and “probable” lung cancer deaths into one group and “possible”,

Table 3
Outcome of the separate review of the cause of death.

Lung cancer death	Reviewer 1	Reviewer 2	Level of agreement
	N of 50 (%)	N of 50 (%)	kappa
Definitely or probable	41 (82)	42 (84)	0.65
- Definitely	33 (66)	41 (82)	0.60
- Probable	8 (16)	1 (2)	0.19
Possible	1 (2)	0 (0)	–
Unlikely	1 (2)	0 (0)	–
Definitely not	3 (6)	7 (14)	0.56
Contributory to other CoD	4 (8)	1 (2)	0.38

CoD: cause of death.

Table 4
The causes of death by the reviewers and the official certificates.

CoD review ^a	Death certificates		
	LC death N (%)	Other CoD N (%)	Total N (%)
LC death	40 (80)	2 (4)	42 (84)
Other CoD	3 (6)	5 (10)	8 (16)
Total	43 (86)	7 (14)	50 (100)

CoD, cause of death; LC, lung cancer.

^a Cause of death after consensus meeting of the reviewers.

“unlikely” and “definitely not” lung cancer death and “intercurrent death” into another, the differences were minimal; agreement in 45 cases (90%) resulting in a kappa of 0.65.

The comparison between the results of the CoD review, after consensus meeting, and the primary cause of death on the official certificates is displayed in Table 4. The sensitivity and specificity of the death certificates are 95.2% (95% confidence interval: 84.2–98.7%) and 62.5% (95% confidence interval: 30.6–86.3%), respectively. Disagreement was observed in 10% (5 of 50 individuals) with the following causes of death: adult respiratory distress syndrome after lobectomy, rupture of an abdominal aneurysm during chemotherapy, another malignancy besides lung cancer in two cases (breast carcinoma and acute myeloid leukaemia) and small cell lung carcinoma diagnosed after the person's death by autopsy.

Autopsy was performed in 3 (6%) of the cases. Five of the 41 (12%) lung cancer deaths involved euthanasia or palliative sedation. The place of death was in the hospital in 48%, in a hospice or nursing home in 10% and at home in 42% of the subjects. In 65% of the cases, the reviewers indicated the letters of the pulmonologist as the most valuable source of information.

4. Discussion

In this pilot study, we have presented the principles of the CoD review process that will be used in the NELSON trial. The pilot study of fifty cases has shown an agreement of 90% (kappa 0.65) between the two reviewers, which demonstrates a reasonable classification. We expect an increase of the level of agreement for the actual review process, performed by clinical experts, with the number of cases they evaluate; the so-called ‘learning-effect’.

When comparing to the CoD process, the sensitivity and specificity of the official death certificates for lung cancer specific mortality were 95.2 and 62.5%, respectively. Despite the lack of a ‘gold standard’ for the cause of death of lung cancer participants, this still demonstrates, in our opinion, a limited distinctive character of the official cause of death certification in lung cancer patients for scientific purposes.

Potential limitations of the present study relate to the sample size and the selection of the subjects of the pilot study. We have taken the first fifty consecutive deceased participants that were diagnosed with lung cancer. This has introduced a selection bias of individuals with a high lung cancer disease stage at diagnosis (Table 2) compared with the screen-arm of the trial [4]. In the pilot study, most deaths were due to lung cancer. It is plausible that death due to other causes than lung cancer plays a bigger part when the files of all NELSON participants will be reviewed. Hence, the figures demonstrated in the pilot could differ from those of the entire study.

No other lung cancer CT screening trial has published results of their methodology of CoD evaluation yet, to our knowledge. In the chest X-ray screening trials, such as the Mayo Lung Project, Hopkins and Sloan-Kettering Lung Trials and the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial, an expert review panel determined the CoD [11,18–20]. Lung cancer mortality was 5–6% overestimated in the intervention arm and 2% underestimated in the usual-care arm by the death certificates in these trials [11,18]. In this initial pilot, the misestimate is 10%.

5. Conclusion

Our and other studies' results imply that the outcome of a lung cancer screening trial cannot reliably be established without a concordance analysis between vital statistics and a CoD review of blinded cases. Moreover, the principles and flowcharts presented here aim to provide one of the essential tools to make data pooling with other CT screening trials in the future possible.

Conflict of interest statement

Roche diagnostics provided a grant for the performance of proteomics-research. Siemens Germany provided four digital workstations and LungCARE for the performance of 3D-measurements.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.lungcan.2012.04.018>.

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